Constraining binding hot spots: NMR and MD simulations provide a structural explanation for enthalpy-entropy compensation in SH2-ligand binding

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SUPPLEMENTARY INFORMATION

Full reference #45

Brooks, B. R.; Brooks, C. L.; Mackerell, A. D.; Nilsson, L.; Petrella, R. J.; Roux, B.; Won, Y.; Archontis, G.; Bartels, C.; Boresch, S.; Caflisch, A.; Caves, L.; Cui, Q.; Dinner, A. R.; Feig, M.; Fischer, S.; Gao, J.; Hodoscek, M.; Im, W.; Kuczera, K.; Lazaridis, T.; Ma, J.; Ovchinnikov, V.; Paci, E.; Pastor, R. W.; Post, C. B.; Pu, J. Z.; Schaefer, M.; Tidor, B.; Venable, R. M.; Woodcock, H. L.; Wu, X.; Yang, W.; York, D. M.; Karplus, M. *J. Comput. Chem.* **2009,** *30*, 1545-1614.

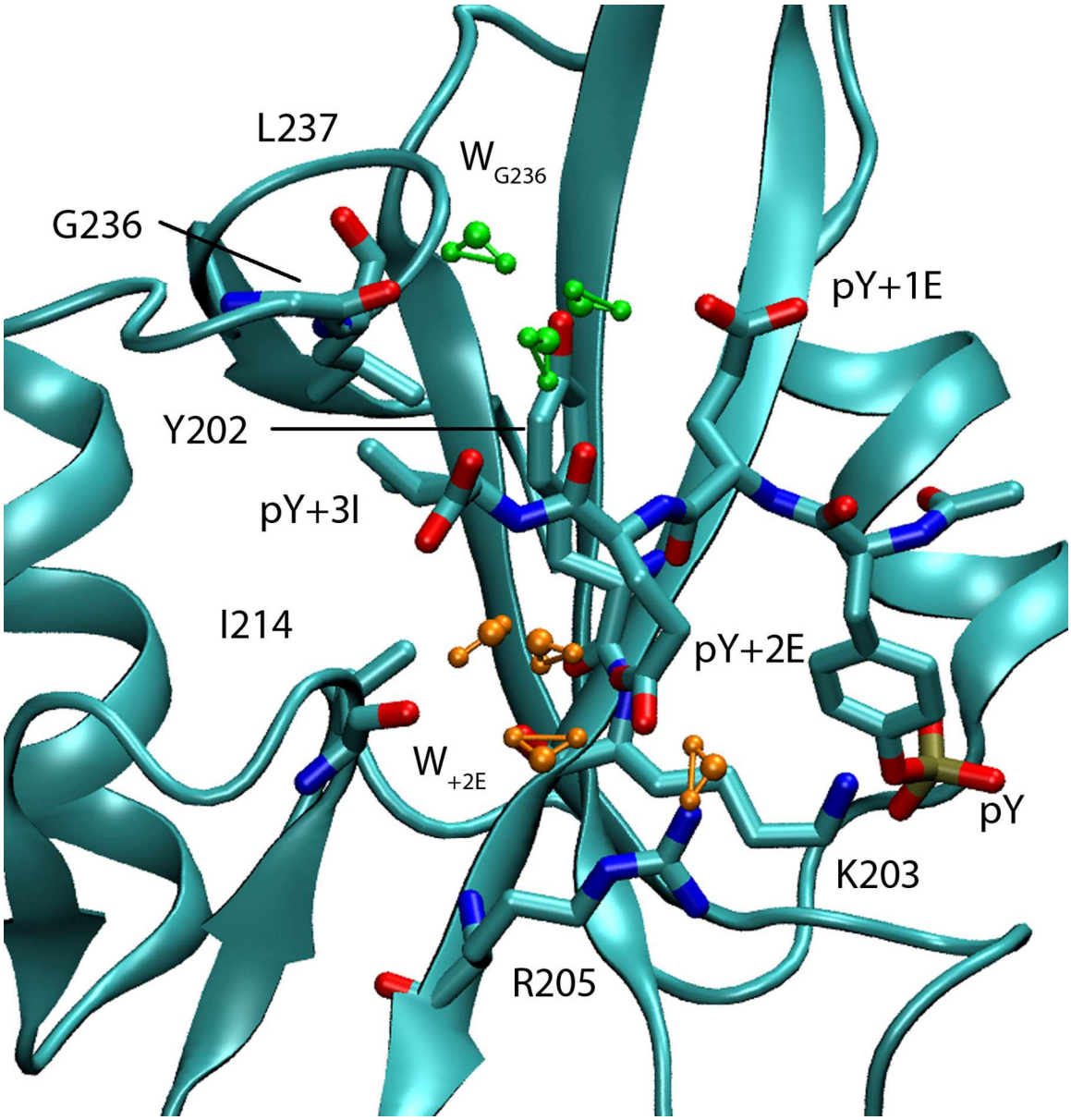

Figure S1. Structural view of the hydrophobic binding pocket illustrating the examined interfacial water molecules as explained in Materials and Methods. W_{G236} (green) denotes water molecules in each molecular dynamics snapshot with oxygen atoms located within 6.0 Å of non-hydrogen atoms of Y202 and G236 or L237. W_{+2E} (orange) denotes water molecules in each snapshot with oxygen atoms located within 3.2 Å of non-hydrogen atoms of both pY+2E and R205, as well as within 6.0 Å of both the K203 and I214 main-chain heavy atoms.

Table S1. Chemical shift differences for main-chain ^{15}N-HSQC peaks and reported mutant binding thermodynamics for important residues

Residue	fpY-pY CSD[a]	cpY-pY CSD[a]	cpY-fpY CSD[a]	Atoms	Mutation	ΔΔG[b]	ΔΔH[b]	TΔΔS[b]
pY					pY to Y[c]	~ 6	~ 4	~ -2
I153	0.034	0.053	0.087	N-H				
T154 (αA1)	0.054	0.027	0.080	N-H				
R155 (αA2)	0.033	0.028	0.048	N-H	R to A[c]	1.1	3.0	1.9
	0.007	0.010	0.015	Nε-Hε				
R175 (βB5)	0.023	0.034	0.057	N-H	R to A[c]	3.2	4.1	0.9
	0.059	0.057	0.106	Nε-Hε				
	0.255	0.332	0.586	Nη-Hη				
E176 (βB6)	0.041	0.083	0.118	N-H				
S177 (βB7)	0.060	0.135	0.188	N-H	S to A[c]	0.9	-1.6	-2.5
E178 (BC1)	0.278	0.281	0.558	N-H	E to A[c]	0.4	0.6	0.2
T179 (BC2)	0.144	0.046	0.184	N-H	T to A[c]	0.9	-0.2	-1.1
T180 (BC3)	0.054	0.114	0.068	N-H	T to A[c]	-0.2	-1.4	-1.2
C185 (βC3)	0.047	0.112	0.155	N-H	C to A[c]	-1.1	0.1	1.2
					C to S[c]	-0.8	0.0	0.8
L186 (βC4)	0.095	0.231	0.326	N-H				
S187 (βC5)	0.008	0.065	0.072	N-H	S to A[c]	0.2	1.0	0.8
K200 (βD3)	0.022	0.032	0.051	N-H	K to A[d]	1.2	2.0	0.8
H201 (βD4)	0.072	0.049	0.116	N-H	H to A[c]	0.3	-0.7	-1.0
Y202 (βD5)	0.065	0.129	0.096	N-H	Y to I[d]	2.1	5.1	3.0
K203 (βD6)	0.018	0.068	0.069	N-H	K to A[c]	1.4	1.5	0.1
I204 (βD7)	0.042	0.114	0.156	N-H				
R205 (βD'1)	0.021	0.019	0.032	N-H	R to A[d]	0.6	0.1	-0.5
	0.012	0.036	0.024	Nε-Hε	R to F[d]	0.3	-0.3	-0.6
I214 (βE4)	0.007	0.025	0.021	N-H	I to A[d]	0.3	-1.4	-1.7
T215 (EF1)	0.021	0.055	0.073	N-H	T to A[d]	0.1	1.2	1.1
S216 (EF2)	0.053	0.174	0.227	N-H				
R217 (EF3)	0.009	0.016	0.018	N-H	R to A[d]	0.2	0.7	0.5
T218	0.030	0.108	0.137	N-H				
D235 (BG2)	0.017	0.041	0.058	N-H	D to A[d]	-0.2	-0.1	0.1
G236 (BG3)	0.027	0.101	0.128	N-H				
L237 (BG4)	0.030	0.100	0.129	N-H	L to A[d]	0.6	-1.2	-1.8
C238 (BG5)	0.019	0.048	0.067	N-H				

a) ppm

b) relative to wild type, in kcal/mol

c) Bradshaw, J. M.; Mitaxov, V.; Waksman, G. *J. Mol. Biol.* **1999,** *293*, 971-985.

d) Bradshaw, J. M.; Mitaxov, V.; Waksman, G. *J. Mol. Biol.* **2000,** *29*, 521-535.

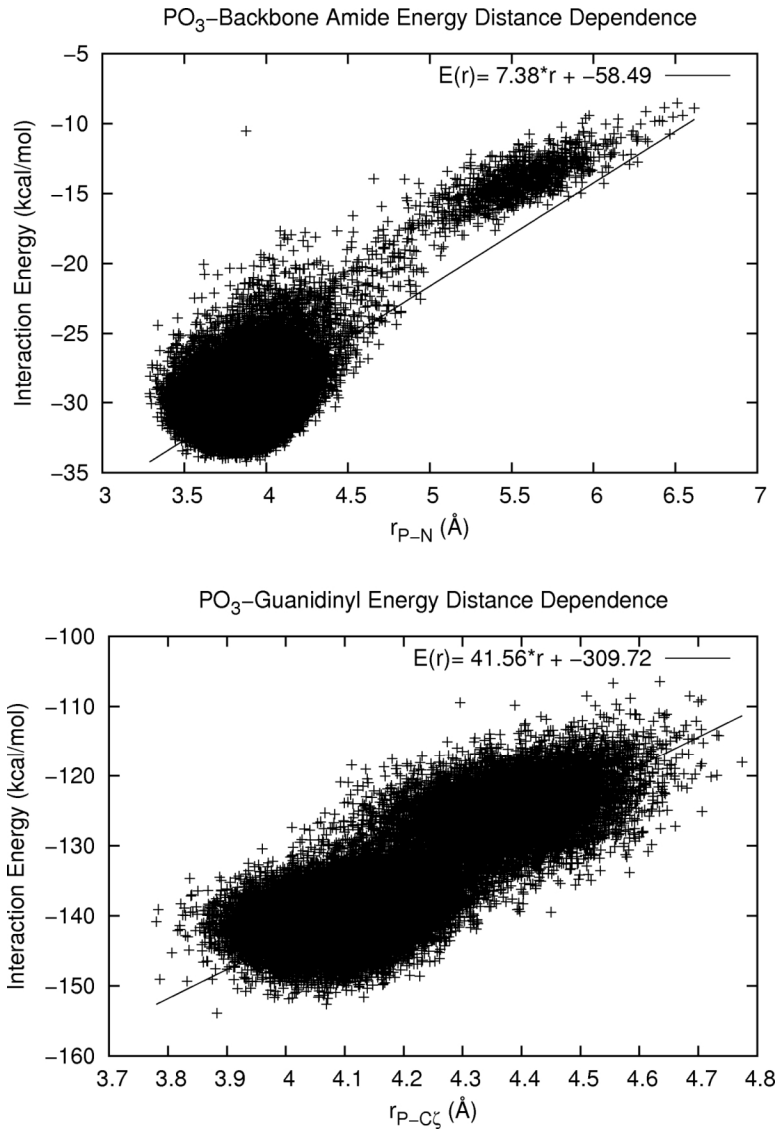

Figure S2. The distance dependence of phosphoryl interaction energies were calculated from MD simulations of the SH2-pYEEI, SH2-cpYEEI, and SH2-fpYEEI complexes. The distance between the phosphorous atom and the main-chain nitrogen atom of E178 or the guanidinyl Cζ carbon atom of R175, respectively, was calculated for each of 45,000 coordinate snapshots. The non-bond energy between two electrostatically neutral groups was calculated for each snapshot using the CHARMM27 force field. The groups, defined in the CHARMM27 force-field topology include the phosphorous atom, the four oxygen atoms, and the Cζ carbon atom of the pY ring for the "PO_3" group, the main-chain nitrogen atom and hydrogen atom, alpha carbon atom and alpha hydrogen atom for the "backbone amide" group of E178 (top), and the Cζ, three nitrogen atoms and associated hydrogen atoms of the R175 guanadinyl group (bottom).

```
* supplementary topology for N,N-dimethyl cylopropancarboxamide model

* J Ward 10 May 2004
*
* Prior to streaming, you must first read:
*     top_all27_prot_na.rtfa, par_all27_prot_na.prm
* and stream supplementary patch file:
*     toppar_prot_na_all.str

read rtf card append
* Topology for trisubstituted cycloproyl derivative peptidomimetics
*
27 1

!MASS   100 C3    12.01100 C ! cyclopropane carbon

DECL -CA
DECL -C
DECL -O
DECL +N
DECL +HN
DECL +CA

RESI C3    0.00          ! Cyclopropane
GROUP                    !
ATOM C1   C3    -0.18    !
ATOM C2   C3    -0.18    !        H4  H7
ATOM C3   C3    -0.18    !         \  /
ATOM H4   HB     0.09    !          C1
ATOM H5   HB     0.09    !         /  \
ATOM H6   HB     0.09    !   H5--C2----C3--H6
ATOM H7   HB     0.09    !         |    |
ATOM H8   HB     0.09    !       H8    H9
ATOM H9   HB     0.09    !
BOND C1 C2  C2 C3  C3 C1  C1 H4  C1 H7  C2 H5  C2 H8  C3 H6  C3 H9
PATCHING FIRST NONE LAST NONE

RESI NMCA       0.00  ! N-methyl cyclopropanecarboxamide
GROUP                 !   Model compund
ATOM C1   C3   -0.18  !      J Ward  25 May 2004
ATOM C2   C3   -0.18  !
ATOM C3   C3   -0.09  !      H8  H11     H14  H15
ATOM C4   C     0.51  !       \  /         \  /
ATOM O5   O    -0.51  !        C1    O5    C7
ATOM N6   NH1  -0.47  !       /  \   ||   /  \
ATOM C7   CT3  -0.11  !  H9--C2--C3--C4--N6   H16
ATOM H8   HB    0.09  !      |    |       \
ATOM H9   HB    0.09  !     H12  H10       H13
ATOM H10  HB    0.09  !
ATOM H11  HB    0.09  !
ATOM H12  HB    0.09  !
ATOM H13  H     0.31  !
ATOM H14  HA    0.09  !
ATOM H15  HA    0.09  !
ATOM H16  HA    0.09  !
BOND C1 C2  C2 C3  C1 C3  C3 C4  C4 N6  N6 C7  C7 H14  C7 H15  C7 H16
BOND C1 H8  C2 H9  C3 H10  C1 H11  C2 H12  N6 H13
DOUBLE C4 O5
IMPR C4 C3 N6 O5  N6 C4 C7 H13
PATCHING FIRST NONE LAST NONE

RESI DMCA       0.00  ! N,N-dimethyl cyclopropanecarboxamide
GROUP                 !   Model compund
ATOM C1   C3   -0.18  !      J Ward 10 May 2004
ATOM C2   C3   -0.18  !
ATOM C3   C3   -0.09  !      H9  H12     H14  H15
ATOM C4   C     0.51  !       \  /         \  /
ATOM O5   O    -0.51  !        C1    O5    C7--H16
ATOM N6   NH1  -0.32  !       /  \   ||   /
ATOM C7   CT3  -0.11  ! H10--C2--C3--C4--N6
ATOM C8   CT3  -0.11  !      |    |       \
```

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ATOM H9   HB    0.09  !     H13  H11       C8--H17
ATOM H10  HB    0.09  !                   /  \
ATOM H11  HB    0.09  !                 H19   H18
ATOM H12  HB    0.09  !
ATOM H13  HB    0.09  !
ATOM H14  HA    0.09  !
ATOM H15  HA    0.09  !
ATOM H16  HA    0.09  !
ATOM H17  HA    0.09  !
ATOM H18  HA    0.09  !
ATOM H19  HA    0.09  !
BOND C1 C2  C1 C3  C2 C3  C3 C4  C4 N6  N6 C7  N6 C8
BOND C1 H9  C2 H10  C3 H11  C1 H12  C2 H13
BOND C7 H14  C7 H15  C7 H16  C8 H17  C8 H18  C8 H19
DOUBLE C4 O5
IMPR C4 C3 N6 O5  N6 C4 C7 C8
PATCHING FIRST NONE LAST NONE

RESI PCP        0.00   !  para-cyclopropyl phenol
GROUP                  !   Model compund
ATOM C1   C3    -0.18  !      J Ward  24 Mar 2004
ATOM C2   C3    -0.18  !
ATOM C3   C3    -0.09  !
ATOM C4   CA     0.000 !      H11 H14  H16  H17
ATOM C5   CA    -0.115 !       \  /     |    |
ATOM C6   CA    -0.115 !        C1      C5--C6
ATOM C7   CA     0.110 !       /  \    //    \\
ATOM C8   CA    -0.115 ! H12--C2--C3--C4     C7--O10
ATOM C9   CA    -0.115 !     /     |   \      /     \
ATOM O10  OH1   -0.54  !   H15    H13   C9==C8      H20
ATOM H11  HB     0.09  !               |    |
ATOM H12  HB     0.09  !              H19  H18
ATOM H13  HB     0.09  !
ATOM H14  HB     0.09  !
ATOM H15  HB     0.09  !
ATOM H16  HP     0.115 !
ATOM H17  HP     0.115 !
ATOM H18  HP     0.115 !
ATOM H19  HP     0.115 !
ATOM H20  H      0.43  !
BOND C1 C2  C2 C3  C1 C3  C3 C4  C5 C6  C7 C8  C4 C9  C7 O10
BOND C1 H11  C1 H14  C2 H12  C2 H15  C3 H13  C5 H16  C6 H17
BOND C8 H18  C9 H19  O10 H20
DOUBLE C4 C5  C6 C7  C8 C9
PATCHING FIRST NONE LAST NONE
```

```
RESI PTC          0.00  ! Constrained phosphotyrosine residue (cpY)
GROUP                   ! Copied from PRES CT3 in top_all27_prot_na.rtf
ATOM C1   C       0.51  !  N-Methylamide C-terminus
ATOM O1   O      -0.51  !  Appropriate name changes made, atom types
GROUP                   !  and charges left alone
ATOM C2   CT3    -0.11  !
ATOM H21  HA      0.09  !
ATOM H22  HA      0.09  !
ATOM H23  HA      0.09  !  The rest is based on RESI TYR, (N->C7)
ATOM N1   NH1    -0.47  !
ATOM H1   H       0.31  !
GROUP
ATOM C7   C3     -0.09  !
ATOM H7   HB      0.09  !      |         HD1  HE1
GROUP                   !   O=C           |    |
ATOM CA   C3     -0.09  !      |   HB    CD1--CE1
ATOM HA   HB      0.09  !      |   |   //       \\
GROUP                   !  HA-CA--CB--CG       CZ--OH
ATOM CB   C3     -0.09  !      |  /     \  __   /     \
ATOM HB   HB      0.09  !  H7-C7/       CD2--CE2     HH
GROUP                   !      |          |    |
ATOM CG   CA      0.00  !  O1=C1         HD2  HE2
GROUP                   !      |
ATOM CD1  CA     -0.115 !  H1-N1
ATOM HD1  HP      0.115 !      |
GROUP                   ! H21-C2-H22
ATOM CE1  CA     -0.115 !      |
ATOM HE1  HP      0.115 !     H23
GROUP
ATOM CZ   CA      0.11
ATOM OH   OH1    -0.54
ATOM HH   H       0.43  !  Will need to apply TP2 patch to model the
GROUP                   !  phosphorylated drug
ATOM CD2  CA     -0.115
ATOM HD2  HP      0.115
GROUP
ATOM CE2  CA     -0.115
ATOM HE2  HP      0.115
GROUP
ATOM C    C       0.51
ATOM O    O      -0.51
BOND CB  CA   CG  CB   CD2 CG   CE1 CD1  C2 H21  C2 H22  C2 H23
BOND CZ  CE2  OH  CZ   C7  CA   C7  C1    C7  CB
BOND N1  H1   N1  C1   C   CA   C   +N   N1  C2
BOND CA  HA   CB  HB  C7  H7   CD1 HD1  CD2 HD2
BOND CE1 HE1  CE2 HE2  OH  HH
DOUBLE C O  C1 O1  CG CD1  CD2 CE2  CE1 CZ
IMPR C1 C7 N1 O1  C CA +N O
IC +N   O    *C   CA    1.3510  31.0000  180.0000 122.0000  1.4950
IC CB   C    *CA  HA    1.4950  31.0000  150.0000 118.0000  1.0760
IC C7   CB   *CA  HA    1.5080  60.0000  105.0000 116.5000  1.0760
IC C    CA   C7   C1    1.4950 117.0000 -140.0000 118.0000  1.4970
IC C7   CA   *CB  HB    1.5080  60.0000  103.0000 113.5010  1.0760
IC C7   HB   *CB  CG    1.0760  40.0000  148.0000 115.0000  1.5000
IC C1   CB   *C7  H7    1.4950  29.0000 -148.0000 115.0000  1.0760
IC O1   C1   C7   H7    1.2020 123.0000 -161.0000 116.0000  1.0760
IC N1   C7   *C1  O1    1.3520  31.0000 -179.0000 123.0000  1.2020
IC O1   C1   N1   H1    1.2020 122.0000  180.0000 122.0000  0.9930
IC C1   H1   *N1  C2    1.3520  33.5000  180.0000 118.5000  1.3530
IC C1   N1   C2   H21   1.3520 119.0000  180.0000 109.6000  1.0760
IC H21  N1   *C2  H22   1.0760 109.6000  120.0000 119.0000  1.0760
IC H21  N1   *C2  H23   1.0760 109.6000 -120.0000 119.0000  1.0760
IC CA   CB   CG   CD1   1.5606 112.9400   90.0000 120.4900  1.4064
IC CD1  CB   *CG  CD2   1.4064 120.4900 -176.4600 120.4600  1.4068
IC CB   CG   CD1  CE1   1.5113 120.4900 -175.4900 120.4000  1.4026
IC CE1  CG   *CD1 HD1   1.4026 120.4000  178.9400 119.8000  1.0814
IC CB   CG   CD2  CE2   1.5113 120.4600  175.3200 120.5600  1.4022
IC CE2  CG   *CD2 HD2   1.4022 120.5600 -177.5700 119.9800  1.0813
IC CG   CD1  CE1  CZ    1.4064 120.4000   -0.1900 120.0900  1.3978
IC CZ   CD1  *CE1 HE1   1.3978 120.0900  179.6400 120.5800  1.0799
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```
IC CZ   CD2  *CE2 HE2   1.3979 119.9200 -178.6900 119.7600  1.0798
IC CE1  CE2  *CZ  OH    1.3978 120.0500 -178.9800 120.2500  1.4063
IC CE1  CZ   OH   HH    1.3978 119.6800  175.4500 107.4700  0.9594
PATCHING FIRST NONE LAST NONE

PRES SM1          0.00 ! Patch residue to convert TYR to fpY
DELETE ATOM N          ! use in generate statement
DELETE ATOM HN         ! * Edited version of PRES CT3
!DELETE ATOM CA         ! top_all27_protein_lipid.inp
!DELETE ATOM HA         !
GROUP                  ! Apply TP2 patch after generation to add phosphate
ATOM CA   CT1    -0.09 !
ATOM HA   HB      0.09 !
GROUP                  !
ATOM C7   CT2    -0.18 !
ATOM H71  HA      0.09 !
ATOM H72  HA      0.09 !
GROUP                  !      |
ATOM C1   C       0.51 !  H71-C7-H72
ATOM O1   O      -0.51 !      |
GROUP                  !     C1=O1
ATOM N1   NH1    -0.47 !      |
ATOM H1   H       0.31 !     N1-H1
ATOM C2   CT3    -0.11 !      |
ATOM H21  HA      0.09 !  H21-C2-H23
ATOM H22  HA      0.09 !      |
ATOM H23  HA      0.09 !     H22
                       !
BOND C7 CA  C7 H71  C7 H72  C7 C1  C1 N1  N1 C2  C2 H21  C2 H22
BOND N1 H1  C2 H23
DOUBLE C1 O1
!DIHE C7 C1 N1 C2
IMPR N1 C1 C2 H1  C1 C7 N1 O1
DONOR H1  N1
IC C7   C    *CA  HA    1.4501 106.5200 -116.0400 107.1500  1.0833
IC C1   CA   *C7  H71   1.5000 112.9400  120.0000 109.6000  1.0760
IC C1   H71  *C7  H72   1.5000 112.9400 -120.0000 109.6000  1.0760
IC CA   C7   C1   O1    1.5000 118.0000 -160.0000 123.0000  1.5000
IC N1   C7   *C1  O1    1.3520  31.0000 -179.0000 123.0000  1.2020
IC O1   C1   N1   H1    1.2020 122.0000  180.0000 122.0000  1.3530
IC C1   H1   *N1  C2    1.3520  33.5000  180.0000 118.5000  1.3530
IC C1   N1   C2   H21   1.3520 119.0000  180.0000 109.6000  1.0760
IC H21  N1   *C2  H22   1.0760 109.6000  120.0000 119.0000  1.0760
IC H21  N1   *C2  H23   1.0760 109.6000 -120.0000 119.0000  1.0760

PRES SM2          0.00 ! Methyl group for inhibitors 5 and 7
DELETE ATOM H1         ! from Davidson et al, JACS (2002) 124(2):205
                       !  Modified from PRES ACE
GROUP                  !   top_all27_prot_na.rtf
ATOM N1   NH1    -0.32 !
ATOM C2   CT3    -0.11 !
ATOM H21  HA      0.09 !
ATOM H22  HA      0.09 !
ATOM H23  HA      0.09 !
ATOM C3   CT3    -0.11 !
ATOM H31  HA      0.09 !      H33
ATOM H32  HA      0.09 !       |
ATOM H33  HA      0.09 !  H31-C3-H32
                       !       |
                       !
BOND C3 N1  C3 H31  C3 H32  C3 H33
ANGL N1 C3 H31  N1 C3 H32  N1 C3 H33  H31 C3 H32  H31 C3 H33  H32 C3 H33
DIHE C1 N1 C3 H31  C1 N1 C3 H32  C1 N1 C3 H33  O1 C1 N1 C3  C3 N1 C1 C7
IMPR N1 C1 C2 C3
IC C1   C2   *N1  C3    1.3520  33.5000  180.0000 118.5000  1.3530
IC C1   N1   C3   H31   1.3520 122.3700   19.1200 109.6000  1.0760
IC C1   N1   C3   H32   1.3520 122.3700  137.7520 109.6000  1.0760
IC C1   N1   C3   H33   1.3520 122.3700 -102.3930 109.6000  1.0760

END
```

```
read para card append
* additional parameters for trisubstituted cyclopropyl derivative
* peptidomimetics
*

BONDS
C3   C3    210.000     1.5010 !  cyclopropane optimization
                !                   JMW  18 Jun 04
C3   HB    360.000     1.0830 !  cyclopropane optimization
                !                   JMW  18 Jun 04
C3   C     200.000     1.4900 !  JMW   21 Jun 04
                !
C3   CA    200.000     1.4900 !
                !                 JMW   21 Jun 04

ANGLES
C3   C3   C3    30.000     60.00    0.00   1.50000 !
                !   cyclopropane optimization  JMW 18 Jun 04
C3   C3   HB    26.000    118.13    4.00   2.22000 !
                !   cyclopropane optimization  JMW 18 Jun 04
HB   C3   HB    24.200    114.04    0.50   2.51000 !
                !   cyclopropane optimization  JMW  18 Jun 04
C3   C3   C     62.000    117.86    0.00   2.56000 !
                !                                  JMW  21 Jun 04
HB   C3   C     43.000    115.00    0.00   2.20000 !
                !                                  JMW  21 Jun 04
C3   C    O     40.000    121.25    0.00   2.36000 !
                !                                  JMW  21 Jun 04
C3   C    NH1   50.000    119.40    0.00   2.44000 !
                !                                  JMW  21 Jun 04
CT3  NH1  CT3   35.000    116.91    0.00   2.47000 !
                !                                  JMW  21 Jun 04
C3   CA   CA    30.000    121.36    !
                !                                  JMW  21 Jun 04
HB   C3   CA    30.000    112.94    !
                !                                  JMW  21 Jun 04
C3   C3   CA    40.000    122.31    !
                !                                  JMW  21 Jun 04
CT2  CT1  CT2   53.350    111.00    8.00   2.56100 !
                !          Assigned by analogy JMW  22 Jun 04
CT1  CT2  C     52.000    108.00    !
                !          Assigned by analogy JMW  22 Jun 04

DIHEDRALS
X    C3   C3   X        1.0000  3   180.00  !
                !   cyclopropane optimization  JMW  18 Jun 04
C3   C3   C    O        1.8000  1   180.00  !
                !                                  JMW  21 Jun 04
HB   C3   C    O        0.9000  2   180.00  !
                !                                  JMW  21 Jun 04
C3   C3   C    NH1      0.0000  3     0.00  !
                !                                  JMW  21 Jun 04
HB   C3   C    NH1      0.0000  1     0.00  !
                !                                  JMW  21 Jun 04
C3   C    NH1  CT3      2.5000  4   180.00  !
                !                                  JMW  21 Jun 04
C3   C    NH1  CT1      2.5000  4   180.00  !
                ! Assigned by analogy to above JMW  22 Jun 04
C3   C    NH1  H        2.5000  2   180.00  !
                !                                  JMW  21 Jun 04
CT3  NH1  CT3  HA       0.0000  1     0.00  !
                !                                  JMW  21 Jun 04
C3   C3   CA   CA       0.7300  2   180.00  !
                !                                  JMW  21 Jun 04
HB   C3   CA   CA       0.1000  3     0.00  !
                !                                  JMW  21 Jun 04
C3   CA   CA   CA       0.0000  1     0.00  !
                !                                  JMW  21 Jun 04
HP   CA   CA   C3       0.0000  1     0.00  !
                !                                  JMW  21 Jun 04
CT1  CT2  C    O        1.4000  1     0.00  !
```

```
                !          Assigned by analogy JMW  22 Jun 04
CT1  CT2  C     NH1      0.0000  1     0.00  !
                !          Assigned by analogy JMW  22 Jun 04

IMPRopers
!  PTC parameters  by JMW
NH1  C     CT3  CT3      0.5000         0    180.0000 ! SMI 5 & 7
                !                 optimized     JMW  21 Jun 04
NH1  X     X    CT3      1.0000         0      0.0000 ! SMI 5 & 7
                !                 optimized     JMW  21 Jun 04

NONBONDED nbxmod  5 atom cdiel shift vatom vdistance vswitch -
cutnb 14.0 ctofnb 12.0 ctonnb 10.0 eps 1.0 e14fac 1.0 wmin 1.5
                !adm jr., 5/08/91, suggested cutoff scheme
C3     0.000000  -0.020000     2.275000 ! cyclopropane JMW  16 april 04
end
```